UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/508,251	04/10/00	FUKUSHIMA	N 065678/0101

HM22/0418

STEPHEN B MAEBIUS
FOLEY & LARDNER
3000 K STREET NW SUITE 500
WASHINGTON HARBOUR
WASHINGTON DC 20007-5109

EXAMINER	
HELMS, L	
ART UNIT	PAPER NUMBER
1642	8

DATE MAILED: 04/18/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/508,251	Fukushima et al
Examiner	**Group Art Unit**
Larry R. Helms Ph.D.	1642

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-12* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-12* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ NOTICE TO COMPLY WITH SEQUENCE REQUIREMENTS

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 1-12 are pending and under examination.

Sequence Requirement

2. Although this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2), an action on the merits could be performed in order to expedite compact prosecution because the claims do not encompass any sequence disclosures. However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Any questions regarding compliance with the sequence rules requirements specifically should be directed to the departments listed at the bottom of the Notice to Comply.

APPLICANT IS GIVEN THE TIME ALLOTTED IN THIS LETTER WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.R.F. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for

response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18 - 892

4. Claims 2, 6, 8, and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 2, 6, 8, and 12 are indefinite for reciting "a low molecular weight compound" because the metes and bounds of the claim cannot be determined. A "low molecular weight compound" can be anything, a peptide, an organic molecule, an inorganic molecule, a DNA fragment, a plastic, a carbohydrate, etc. Applicant's attention is directed to Ex Parte Tanksley (26 USPQ2d 1384) wherein the Board noted that under 35 U.S.C. 112, second paragraph, the claims must be so definite as to allow the comparison with the available art and must also make it possible for the public to determine from the claims what they encompass. How would one skilled in the art be able to determine the metes and bounds of the claims?

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 2, 6, 8, and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 2, 6, and 12 have been amended to recite "A fragment of a monoclonal antibody, a peptide or a low molecular weight compound". The response filed 9/8/00 did not state where support for the limitations are in the specification or the claims as originally filed. The response filed 2/8/01 stated that support can be found on pages 15-16. The specification discloses on page 15-16 that the monoclonal antibodies described above also encompass peptides and low molecular weight compounds. This is not sufficient because support needs to be provided by the specification as originally filed. Claims 2, 6, and 12 have been amended to change the scope of the claims by removing the phrase "of a monoclonal antibody". Applicant is required to either point to where the specification provides support for the phrase or to remove it from the claims.

7. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a monoclonal antibody or antigen binding fragments of a monoclonal antibody that induces apoptosis of jurkat and HL-60 cells wherein the antibody binds the antigen integrin associated protein (IAP), does not reasonably provide enablement for any antibody that induces apoptosis of any nucleated blood cells or that does not bind to the IAP, or any

antileukemic agent, or any peptide or fragment of an antibody or any low molecular weight compound that induces apoptosis of any nucleated blood cells having IAP, or any fragment, peptide, or low molecular weight compound of a monoclonal antibody that induces apoptosis that does not bind IAP. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to any antibody that induces apoptosis of nucleated blood cells which have the IAP wherein the antibody does not bind to IAP, or any antileukemic agent, or any peptide or any low molecular weight compound that induces apoptosis of nucleated blood cells which have the IAP wherein the peptide or low molecular weight compound does not bind to IAP, or any fragment of an antibody that does not bind IAP.

The specification teaches the production of monoclonal antibodies and antigen binding fragments of monoclonal antibodies (see pages 15-16) that induce apoptosis in HL-60 cells and Jurkat cells (see page 25-26) and bind to IAP. The specification does not enable any antibody

other than those that bind to IAP and induce apoptosis in any nucleated blood cells or any antileukemic agent. The specification does not enable any peptide or any low molecular weight compound that induces apoptosis of nucleated blood cells having IAP or any antibody fragment that induces apoptosis of nucleated blood cells having IAP wherein the antibody fragment does not bind IAP.

The claims are not commensurate in scope with the enablement provided in the specification. The claims are broadly drawn to a fragment of an antibody wherein the antibody does not bind antigen. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al.

teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibody fragments as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an antibody, have the required binding function. The specification provides no direction or guidance regarding how to produce fragments or peptides of antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Further, a fragment of a monoclonal antibody can be the heavy chain, a light chain, or can be any one of the constant regions (CH1-3) and also may be the hinge region. However, the language also reads on small amino acid sequences which are incomplete regions of the constant region of the antibody. One of skill in the art would neither expect nor predict the appropriate functioning of the antibody as broadly as is claimed.

Claims 2, 6, and 12 are broadly drawn to any peptide or any low molecular weight compound that induces apoptosis in nucleated blood cells, however, the specification does not enable any peptide or any low molecular weight compound with the claimed properties.

The claims are broadly drawn to any antileukemic agent, which can be an antibody, however, the specification lacks enablement for any antileukemic agent. As evidenced by Stedman's Medical Dictionary (on line) the term "leukemia" is a generic term and encompasses many cells such as mast cells, white blood cells, lymphocytic, myeloid cells, neutrophilic,

eosinophilic, stem cell, etc. As evidenced by the ATCC Cell lines and Hybridoma Catalog of 1994 HL-60 cells are promyelocytic leukemia cells and jurkat cells are Acute T cell leukemia cells (see page 127, 188, and 335). The specification does not teach that the antigen IAP is presented on all of the cells encompassed by the claims or that the "antileukemic agent" functions as claimed on cells other than HL-60 or Jurkat cells.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-3, 7, 8, 9, are rejected under 35 U.S.C. 102(b) as being anticipated by Genestier et al (Blood 90:726-735, 7/1997, IDS #5) as evidenced by the disclosure on page 5, lines 12-18 and Reinhold et al (J. Cell Sci. (1995), 108(11), 3419-25).

a. The claims recite a monoclonal antibody or fragment of a monoclonal antibody that induces apoptosis of nucleated blood cells having human IAP and a hybridoma that produce the antibody.

b. Genestier et al teach an antibody and hybridoma that produces the antibody wherein the antibody induces apoptosis in lymphocytes (see entire document, abstract and Materials and Methods). As evidenced by the specification on page 5, lines 12-18, nucleated blood cells are lymphocytes. As evidenced by Reinhold et al, IAP is expressed on lymphocytes (see abstract).

Conclusions

10. No Claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

SHEELA HUFF
PRIMARY EXAMINER

Application No.: 09/508251

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: _____

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE